

gel layer which supports the differentiation and maturation of human mesenchymal stem cells into chondrocytes. The mesenchymal stem cells are contacted with a chondroinductive agent. As defined in Claim 13, the chondroinductive agent is selected from the group consisting of a glucocorticoid and a member of the transforming growth factor superfamily. A preferred chondroinductive factor is TGF- $\beta$ 3, as defined in Claim 14.

As defined in Claim 15, the composition may further comprise hyaluronic acid.

In another aspect of the present invention, as defined broadly in Claim 18, there is provided a method for regenerating or repairing cartilage in an individual in need thereof by administering to the individual human mesenchymal stem cells in an alginate gel layer which supports the differentiation and maturation of human mesenchymal stem cells into a chondrogenic lineage to an extent sufficient to accelerate cartilage formation therefrom. The mesenchymal stem cells also are contacted with a chondroinductive agent. The chondroinductive agent may be those hereinabove described.

In a further aspect of the present invention, as defined broadly in Claim 23, there is provided a method of forming cartilage *in vitro*. The method comprises admixing human mesenchymal stem cells with a solution comprising alginate. The alginate then is polymerized to form a composition comprising the human mesenchymal stem cells in an alginate gel layer. The human mesenchymal stem cells in an alginate gel layer then are contacted with a chondroinductive agent.

The alginate may be sodium alginate, as defined in Claim 24. The solution may further comprise hyaluronic acid, as defined in Claim 25, and the chondroinductive agent may be those hereinabove described.

Grande discloses mesenchymal stem cells which may be contained in a polymeric matrix, such as polyglycolic acid or alginate. The mesenchymal stem cells and the carrier may be implanted into a cartilage and/or bone defect, whereby the mesenchymal stem cells will differentiate into bone or cartilage. Grande, however, does not disclose or even remotely suggest to one of ordinary skill in the art that the mesenchymal stem cells are contacted with a

chondroinductive agent. In fact, Grande, at Page 6, lines 14-17, states that an exogenous chondrogenic differentiating factor is not required. Grande also does not disclose or even remotely suggest to one of ordinary skill in the art that hyaluronic acid may be added to the polymeric matrix, as defined in Claim 15.

In addition, Grande, in his working example, i.e., Example 1, describes the implantation of a polyglycolic acid matrix, including mesenchymal stem cells, into the knee joints of rabbits. As indicated at Pages 21 and 22 of Grande, there was little differentiation of the mesenchymal stem cells into cartilage at 6 weeks after implantation, and it was not until 12 weeks after implantation that the polyglycolic acid-mesenchymal stem cell matrix showed a surface layer of cartilage which was approximately the same thickness as the host cartilage. Thus, Grande teaches the *in vivo* differentiation of mesenchymal stem cells into cartilage, and does not even remotely suggest to one of ordinary skill in the art Applicants' claimed method of forming cartilage *in vitro*, as defined in Claim 23.

Thus, for the above reasons and others, Grande does not anticipate Applicants' composition and methods as claimed, nor does Grande render Applicants' composition and methods as claimed obvious to one of ordinary skill in the art. It is therefore respectfully requested that the rejection under 35 U.S.C. 102(b) be reconsidered and withdrawn.

Claims 1, 6, 7, and 9-11 had stood rejected under 35 U.S.C. 103 as being unpatentable over Borland, et al. in view of Grande, et al. This rejection is respectfully traversed.

The differences between Applicants' composition as claimed and Grande have been mentioned hereinabove.

Borland discloses compositions for implantation into an animal which in general includes a biodegradable polymer, and which also may include living cells. The biodegradable polymer may be alginate, and the polymer may contain mesenchymal stem cells. Borland, like Grande, however, does not disclose or even remotely suggest to one of ordinary skill in the art that the mesenchymal stem cells are contacted with a chondroinductive agent. Borland also does not

disclose or even remotely suggest to one of ordinary skill in the art that the polymer also may include hyaluronic acid.

Therefore, the combination of Borland and Grande does not disclose or even remotely suggest to one of ordinary skill in the art a composition for producing cartilage which comprises human mesenchymal stem cells in an alginate layer which supports the differentiation and maturation of human mesenchymal stem cells into chondrocytes, and wherein the mesenchymal stem cells are contacted with a chondroinductive agent, or a method for regenerating or repairing cartilage in an individual by administering such a composition to an individual, or Applicants' claimed method of forming cartilage *in vitro*. Therefore, the combination of Borland and Grande does not render Applicants' composition and methods as claimed obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejection under 35 U.S.C. 103 be reconsidered and withdrawn.

Claims 2-5 and 8 stood rejected under 35 U.S.C. 103 as being unpatentable over Grande, et al. in view of Pittenger, et al.

Claims 2-5 and 8 stood rejected under 35 U.S.C. 103 as being unpatentable over Borland, et al. in view of Grande, et al., and further in view of Pittenger, et al.

These rejections are respectfully traversed.

Grande and Borland have been discussed hereinabove. These references do not disclose or suggest Applicants' composition and method as claimed of one of ordinary skill in the art.

Pittenger discloses the culturing of mesenchymal stem cells in the presence of a high-glucose chondrogenic medium which also includes a transforming growth factor, and in particular TGF- $\beta$ 3, to induce differentiation of the mesenchymal stem cells into chondrocytes. Pittenger, however, does not disclose or even remotely suggest to one of ordinary skill in the art a composition which comprises human mesenchymal stem cells in an alginate gel layer.

Pittenger, at Page 4, lines 7-9, states that the mesenchymal stem cells preferably are condensed together as a packed or pelleted cell mass. In Example 2 of the above-identified application, mesenchymal stem cells were cultured under chondrogenic conditions in pellet format, and in alginate layers in accordance with the present invention. After 21 days under chondrogenic conditions, the cells in the alginate layer were similar morphologically to chondrocytes, and had a homogeneous appearance. The cells in the cell pellets were of variable morphology. Thus, under chondrogenic culturing conditions, the alginate layer provides for improved differentiation of mesenchymal stem cells into chondrocytes, as opposed to the culturing of the mesenchymal stem cells in a cell pellet. Such an improvement clearly was not contemplated by Pittenger.

The Examiner also states that Pittenger, at Page 15, in the first full paragraph, discloses that the mesenchymal stem cells are contacted with hyaluronic acid. The hyaluronic acid in Pittenger, however, is not present in the chondrogenic medium described in Table I on Page 15. The hyaluronic acid referred to by Pittenger is an extracellular matrix component which is produced after the mesenchymal stem cells are cultured in the chondrogenic medium, and not part of the composition for producing cartilage as defined in Claim 15. Thus, Pittenger does not even remotely suggest to one of ordinary skill in the art a composition for producing cartilage which comprises human mesenchymal stem cells in an alginate layer and hyaluronic acid, and wherein the mesenchymal stem cells are contacted with a chondroinductive agent.

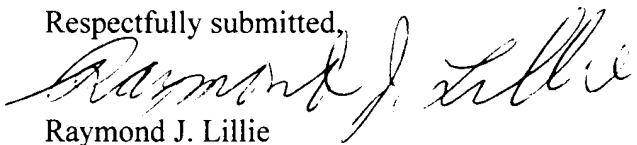
The combination of Pittenger, which does not disclose an alginate layer for supporting the differentiation and maturation of mesenchymal stem cells into chondrocytes, with Grande and Borland would not suggest to one of ordinary skill in the art to provide a composition comprising human mesenchymal stem cells in an alginate gel layer, wherein the mesenchymal stem cells are contacted with a chondroinductive agent, or the use of such a composition to regenerate or repair cartilage, or to form cartilage *in vitro*. At best, the combination of Grande, Borland, and Pittenger would render it obvious to try to provide Applicants' claimed composition and methods; however, such a standard for obviousness is improper. (See American Hospital Supply Corp. v. Travenol Laboratories, Inc., 223 U.S.P.Q. 577 (C.A.F.C. 1984), at 582; In Re Dow Chemical, 5 U.S.P.Q.2d 1529 (C.A.F.C. 1988), at 1531.) Thus, for the above reasons and others, the combination of Grande, Borland, and Pittenger does not render Applicants'

composition and methods as claimed obvious to one of ordinary skill in the art, and it is therefore respectfully requested that the rejections under 35 U.S.C. 103 be reconsidered and withdrawn.

Regarding the rejections under 35 U.S.C. 112, the claims as amended define a composition in which the human mesenchymal stem cells are in an alginate gel layer, and a method of regenerating or repairing cartilage by administering such composition to an individual in need thereof. The Examiner, in the Office Action, has admitted that such an embodiment as claimed is enabled, and such claims clearly state that the human mesenchymal stem cells are in the alginate layer. For the above reasons and others, the claims are enabled by the specification, and point out particularly and claim distinctly the subject matter Applicants regard as the invention. It is therefore respectfully requested that the rejections under 35 U.S.C. 112 be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Raymond J. Lillie".

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